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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 01/09/2006

Application Number: 09/244,195
Filing Date: 02/04/1999
Appellant(s): Kitto, G. B., and M. S. Burnett

David L. Parker (Reg. No.32,165)
For Appellant

EXAMINER'S ANSWER

This is in response to appellants' brief on appeal filed 24 October, 2005.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellants' statement of the status of amendments after final rejection contained in the brief is correct. The amendment after final rejection filed on 24 October, 2005, has been entered.

(5) Summary of Claimed Invention

The summary of invention contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are

set forth below.

Grounds of Rejection Withdrawn

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner:

1) The previous rejection of claims 6, 8-10, 12, and 13 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, was withdrawn in response to the amendment-after-final submitted 24 October, 2005.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

The following is a listing of the evidence (e.g., patents, publications, Official Notice, and admitted prior art) relied upon in the rejection of claims under appeal:

1) Brey, R. N., *et al.*, 12 May, 1992, "Vaccines for the malaria circumsporozoite protein", U.S. Patent No. 5,112,749.

2) Georgiou, G., *et al.*, 20 September, 1994, "Expression of proteins on bacterial surface", U.S. Patent No. 5,348,867.

3) Hone, D. M., et al., 1996, "Optimization of live oral *Salmonella*-HIV-1 vaccine vectors for the induction of HIV-specific mucosal and systemic immune responses", J. Biotech. 44:203-207.

4) Thimmig, R. L., and C. S. McHenry, 1993, "Human immunodeficiency virus reverse transcriptase", J. Biol. Chem.

268(22):16528-16536.

(9) Grounds of Rejection

The following grounds of rejection are applicable to the appealed claims:

35 U.S.C. § 103(a)

Claims 6, 8-10, 12, and 13 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Brey *et al.* (1992), in view of Georgiou *et al.* (1994) and Thimmig *et al.* (1993). Claim 6 is directed toward a **method** of **initiating** an **immune response** against the **human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT)** or **transactivating (TAT) proteins** by administering to an animal an **attenuated bacterial host** comprising a **recombinant plasmid** that carries a **fusion protein** contruct. The construct encodes a fusion protein comprising a region required for **surface exposure** and the **HIV-1 RT** or **TAT proteins**. It was further stipulated that said bacterial host can induce both cellular and humoral anti-HIV-1 immune responses (IRs). Claim 8 further specifies that the IR comprises both a **T-helper cell** response and a **mucosal IgA** response. Claims 9 and 10 are directed toward the well-known **routes** of **administration** (e.g., oral) and **dosages** (e.g., ~10^{12}-10^{14} CFU). Claim 12 specifies that the surface exposure gene encodes an *Escherichia coli* **lipoprotein signal sequence (Lpp)** linked to a portion of the *E. coli* **outer membrane protein OmpA**. Claim 13 requires the use of a specific attenuated bacterial host (e.g., ***Salmonella typhimurium* strain SL3261**).

The criteria that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are set

forth in *Graham et al. v. John Deere Company of Kansas City et al.; Calmar, Inc. v. Cook Chemical Company; Colgate-Palmolive Company v. Same*, 148 U.S.P.Q. 459 (U.S. Sup. Ct. 1966). These factual inquiries can be summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness (i.e., commercial success, long felt but unsolved needs, failure of others, etc.).

As previously set forth, Brey *et al.* (1992) describe the preparation of **attenuated bacterial (e.g., S. *typhimurium*) expression systems** (including those derived from strain **SL3261**) that are useful for the expression of heterologous (e.g., malaria) antigens. A detailed description of suitable expression vectors can be found in Table 1 and column 20. This publication also discloses that said expression systems are particularly useful because the vectors of interest retain their enteroinvasive properties but are markedly reduced in terms of virulence. This properties make these vectors particularly useful for generating **both humoral** and **cell-mediated immune responses** against the antigen of interest (see col. 7, first paragraph). Various vaccine formulations were prepared and routes of administration utilized (i.e., **oral**, intradermal, intramuscular, intraperitoneal, intranasal, etc.) (see col. 6, lines 36-61; col. 21, section 5.6). A particularly attractive feature of this vector system is the ability of S. *typhimurium* to invade the gut epithelial tissue thereby leading to strong **mucosal** and **helper immune responses** (see cols. 23 and 24,

section 5.6.2). Other advantages of this vector system include the lack of a necessary purification step for the immunogen of interest and the ability of this system to be inexpensively produced and conveniently administered. The probability of adverse reactions in both animals and humans is also low. This teaching does not disclose the utilization of an Lpp-OmpA-RT fusion protein or oral dosages in the range of 10^{12} to 10^{14} CFU *per se* (dosages of 10^{10} were employed).

Georgiou *et al.* (1994) describe the preparation of recombinant DNAs that are suitable for the expression of a heterologous antigen on the external surface of an enteric microorganism (e.g., E. *coli* or Salmonella). DNA constructs were prepared that were capable of encoding fusion proteins comprising the **Lpp signal sequence**, **OmpA coding portion**, and a **heterologous antigen** (i.e., see col. 3, lines 42-63; col. 4, lines 4-37; EXAMPLE 1, cols. 15-16; and Figure 1). The inventors noted that targeting sequences (e.g., Lpp) and membrane traversing amino acid sequences (e.g., OmpA) are well-known in the prior art (see cols. 3 and 4). **The inclusion of these coding sequences in a fusion construct facilitates the expression, transport, and presentation of a heterologous antigen on the cell surface of a gram-negative bacterium.** It was reported that various strains of Salmonella would prove particularly useful for the invention (see col. 5, last paragraph). This teaching does not disclose recombinants expressing the HIV-1 *reverse transcriptase* gene.

Thimmig and colleague provide the complete nucleotide/amino acid sequence of the **HIV-1 RT gene** and expression vectors comprising said gene. For instance, see MATERIALS AND METHODS, p. 16529, and Results, pages 16530-16533, wherein the gene,

expression vectors, and cell lines producing said protein are described. Thus, this teaching clearly illustrates that HIV-1 RT was widely available and of obvious diagnostic and medical importance.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to express the HIV-1 RT gene provided by Thimmig *et al.* (1993), as an Lpp-OmpA-RT fusion protein, as suggested by Georgiou *et al.* (1994), in the S. *typhimurium* expression system described by Brey *et al.* (1992), since Brey and colleagues teach that this system is useful for generating strong humoral and cellular immune responses against the antigen of interest. The skilled artisan would have been motivated to prepare such constructs since this would facilitate the development of HIV-1 RT-specific immunological reagents (i.e., antibodies) which can be employed in diagnostic, immunological, or biochemical assays. It would have also been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to prepare a fusion protein comprising the Lpp signal sequence, OmpA, and HIV-1 RT since Georgiou *et al.* (1994) teach that Lpp-OmpA-X fusion proteins are expressed in large quantities in an antigenic/immunogenic form on the cell surface of enteric bacteria. Suitable dosages and routes of administration that lead to an optimal immune response could be easily achieved through routine experimentation, absent evidence to the contrary. The skilled artisan would expect an enteroinvasive vaccine vector to induce both a mucosal IgA and T-helper immune response because of its ability to invade gut tissue and gain access to mesenteric lymphoid tissue (see Brey *et al.*, 1992; col. 23, lines 47-51).

Claims 6, 8-10, 12, and 13[1] are rejected under 35 U.S.C. § 103(a) as being obvious over Hone *et al.* (1996) in view of Georgiou *et al.* (1994) and Thimmig *et al.* (1993). Claim 6 is directed toward a **method** of **initiating** an **immune response** against the **human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT)** or **transactivating (TAT) proteins** by administering to an animal an **attenuated bacterial host** comprising a **recombinant plasmid** that carries a **fusion protein** contruct. The construct encodes a fusion protein comprising a region required for **surface exposure** and the **HIV-1 RT** or **TAT proteins**. It was further stipulated that said bacterial host can induce both cellular and humoral anti-HIV-1 immune responses (IRs). Claim 8 further specifies that the IR comprises both a **T-helper cell** response and a **mucosal IgA** response. Claims 9 and 10 are directed toward the well-known **routes** of **administration** (e.g., oral) and **dosages** (e.g., ~10^{12}-10^{14} CFU). Claim 12 specifies that the surface exposure gene encodes an *Escherichia coli* **lipoprotein signal sequence (Lpp)** linked to a portion of the *E. coli* **outer membrane protein *ompA***. Claim 13 requires the use of a specific attenuated bacterial host (e.g., ***Salmonella typhimurium* strain SL3261**).

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[1] As previously set forth, the teachings of Hone and colleagues describes the use of an S. *typhimurium* strain carrying a mutation in the *aro* locus. This attenuated bacterial strain appears to be the same strain described by Fouts *et al.* (1995, Construction and immunogenicity of *Salmonella typhimurium* vaccine vectors that express HIV-1 gp120, Vaccine, 13(17):1697-705) which was designated strain SL3261. Since the Patent Office does not have the facilities for examining and comparing applicants' claimed S. *typhimurium* strain SL3261 with the S. *typhimurium* strain employed by Hone *et al.* (1996), the burden is upon applicants to demonstrate the unobvious genotypic/phenotypic differences between the two strains. *In re Best*, 562 F.2d 1252, 195 U.S.P.Q. 430 (C.C.P.A. 1977). *Ex parte Gray*, 10 U.S.P.Q.2d 1922 (Bd. Pat. Appl. Int. 1989).

The criteria that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are set forth in *Graham et al. v. John Deere Company of Kansas City et al.; Calmar, Inc. v. Cook Chemical Company; Colgate-Palmolive Company v. Same*, 148 U.S.P.Q. 459 (U.S. Sup. Ct. 1966). These factual inquiries can be summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness (i.e., commercial success, long felt but unsolved needs, failure of others, etc.).

Hone and colleagues provide attenuated bacterial hosts (e.g., ***Salmonella typhimurium***) vaccine vectors containing expression vectors encoding fusion proteins comprising the *Escherichia coli* **outer membrane protein (OmpA)** and HIV-1 gp120 (e.g., OmpA::gp120). These Salmonella strains induced **both mucosal** and **systemic** HIV-1 gp120-specific immune responses. The authors concluded (see Abstract, p. 203) that "**These results, therefore, support the proposal that *Salmonella* vectors will be a safe and inexpensive means for delivery of HIV antigens to, and the elicitation of HIV-specific T cells in, the mucosal and systemic compartments.**" The authors also noted (p. 206, penultimate paragraph) that "**It is reasonable to propose, therefore, that *Salmonella* bearing surface-expressed rgp120 will elicit gp120-specific CD8$^+$ CTLs.**" This teaching does not disclose **Lpp**-OmpA-HIV-1 **RT** fusion proteins.

Georgiou *et al.* (1994) describe the preparation of recombinant DNAs that are suitable for the expression of a

heterologous antigen on the external surface of an enteric microorganism (e.g., E. *coli* or Salmonella). DNA constructs were prepared that were capable of encoding fusion proteins comprising the **Lpp signal sequence**, **OmpA coding portion**, and a **heterologous antigen** (i.e., see col. 3, lines 42-63; col. 4, lines 4-37; EXAMPLE 1, cols. 15-16; and Figure 1). The inventors noted that targeting sequences (e.g., Lpp) and membrane traversing amino acid sequences (e.g., OmpA) are well-known in the prior art (see cols. 3 and 4). **The inclusion of these coding sequences in a fusion construct facilitates the expression, transport, and presentation of a heterologous antigen on the cell surface of a gram-negative bacterium.** It was reported that various strains of Salmonella would prove particularly useful for the invention (see col. 5, last paragraph). This teaching also discusses **oral** formulations and suitable **dosages** (see col. 13, lines 61-68; col. 14, lines 3-16). This teaching does not disclose recombinants expressing the HIV-1 *reverse transcriptase* gene.

Thimmig and colleague provide the complete nucleotide/amino acid sequence of the **HIV-1 RT gene** and expression vectors comprising said gene. For instance, see MATERIALS AND METHODS, p. 16529, and Results, pages 16530-16533, wherein the gene, expression vectors, and cell lines producing said protein are described. Thus, this teaching clearly illustrates that HIV-1 RT was widely available and of obvious diagnostic and medical importance.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to express the HIV-1 RT gene provided by Thimmig *et al.* (1993), as an Lpp-OmpA-RT fusion protein, as suggested by

Georgiou *et al.* (1994), in the S. *typhimurium* expression system described by Hone *et al.* (1996), since Hone and colleagues teach that this system is useful for generating strong immune responses against the antigen of interest. The skilled artisan would have been motivated to prepare such constructs since this would facilitate the development of HIV-1 RT-specific immunological reagents (i.e., antibodies) which can be employed in diagnostic, immunological, or biochemical assays. It would have also been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to prepare a fusion protein comprising the Lpp signal sequence, OmpA, and HIV-1 RT since Georgiou *et al.* (1994) teach that Lpp-OmpA-X fusion proteins are expressed in large quantities in an antigenic/immunogenic form on the cell surface of enteric bacteria.

(10) Response to Argument

Claims 6, 8-10, 12, and 13 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Brey *et al.* (1992), in view of Georgiou *et al.* (1994) and Thimmig *et al.* (1993). Applicants traverse and submit that the prior art fails to teach or suggest fusion constructs employing RT. This argument is clearly not persuasive. The examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. *In re Nomiya*, 184 U.S.P.Q. 607 (C.C.P.A. 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is

what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. *In re McLaughlin*, 170 U.S.P.Q. 209 (C.C.P.A. 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. *In re Bozek*, 163 U.S.P.Q. 545 (C.C.P.A. 1969). In this case, the prior art clearly provides efficient attenuated enteroinvasive vaccine vectors that induce strong humoral (including mucosal) and cell-mediated immune responses (including T-helper responses) against the immunogen of interest. The prior art clearly illustrates that Lpp-OmpA-X fusion proteins are transported to the surface and placed in a highly immunogenic background. Thus, the only real issue is whether one of ordinary skill in the art would have been motivated to prepare RT fusion constructs using these reagents. The answer to this question is emphatically yes. The human immunodeficiency virus type 1 is the aetiological agent of AIDS. One of ordinary skill in the art would have had more than sufficient motivation to prepare RT fusion constructs because of the medical importance of this virus and gene product. Utilizing the Salmonella expression system would provide a facile means for generating large quantities of an immunogenic protein that will be capable of inducing both humoral and cell-mediated immune response.

Appellants further argue that Brey and associates fail to contemplate or disclose "the treatment of HIV-1" or the generation of an "HIV-1 vaccine". This argument is inapposite since the claims are not directed toward the generation of an HIV-1 vaccine or the treatment of the clinical sequelae associated with HIV-1 infection. The claims simply require the

use of an attenuated bacterial host encoding an Lpp-OmpA-RT or -Tat fusion protein for the induction of both humoral and cellular anti-HIV-1 immune responses. There is no requirement that the composition administered must be protective or therapeutic. Thus, the skilled artisan only needs to be motivated to combine the teachings relied upon to generate a strong immune response against the viral antigen of interest. As set forth *supra*, the skilled artisan would be motivated to generate immunological reagents against RT since these would prove useful in a variety of different formats (i.e., diagnostic assays).

It was further argued that Georgiou and colleagues teach away from the claimed invention because they fail to disclose the use of HIV-1 antigens. This argument is clearly not persuasive. This teaching was relied upon because it unequivocally demonstrates that **Lpp-OmpA-X** gene fusions facilitate the expression, transport, and presentation of heterologous antigens on the cell surface of gram-negative bacterial vaccine vectors.

The teachings of Thimmig and co-workers also fail to discuss the "generation of an HIV-1 vaccine." Once again, appellants are reminded that the claims are not directed toward an HIV-1 vaccine, but simply the generation of an immune response against HIV-1. Such a response could encompass the generation of antibodies for diagnostic purposes (i.e., antigen-capture assays) or biochemical purposes (i.e., affinity purification of viral antigens). There is no requirement that the immune response must be protective or therapeutic. Thus, the arguments presented by appellants are once again inapposite.

Concerning the reliance upon Brey and associates, appellants simply state that this teaching is directed toward the treatment of malaria, not HIV-1. Once again, appellants are reminded that this teaching clearly illustrates the utility of employing attenuated bacterial hosts carrying surface expressed heterologous antigens to induce strong humoral and cell-mediated immune responses. It was already well-established that these vectors (e.g., SL3261) were efficient at inducing mucosal immune responses (see col. 6, lines 36-61). The inventors further add that the present invention is also capable of inducing strong cell-mediated immune responses.

Appellants additionally argue that there is no reasonable expectation of success because of the reference to "failed attempts to elicit an immune response" which would prove useful for the prevention or treatment of disease. Appellants are again reminded that there is no requirement in the claim language that the immune response must be protective in nature. The only stipulation is that the attenuated bacterial host must be capable of inducing both a humoral and cellular immune response against HIV-1. The response does not need to be protective or therapeutic in nature.

It was additionally argued by appellants that the references relied upon fail to disclose the induction of both mucosal IgA and T-helper immune responses. As previously set forth, Brey *et al.* (1992) describe the preparation of attenuated bacterial (e.g., S. *typhimurium*) expression systems (including those derived from strain SL3261) that are useful for the expression of heterologous (e.g., malaria) antigens. A particularly attractive feature of this vector system is the ability of S.

typhimurium to invade the **gut epithelial tissue** thereby leading to strong **mucosal** and **helper immune responses** (see cols. 23 and 24, section 5.6.2). It is well-known in the field of immunology that B-cells produce antibody in response to activated T-helper lymphocytes ($CD4^+$).[2] $CD4^+$ lymphocytes become activated when antigen presenting cells (e.g., macrophages) present antigens to their cell surface. Brey and colleagues clearly disclose that one of the advantages of the attenuated bacterial system is that the enteroinvasive properties of the bacteria allow them to enter the reticuloendothelial system which leads to "an influx of macrophages which ingest the bacteria." These antigen presenting cells deliver the antigen to T-helper lymphocytes which produce IL-2 which results in the activation of B-cells and antibody production.

Appellants further state that the references relied upon fail to teach the claimed dosages (e.g., 10^{12}-10^{14} CFU). Appellants are directed toward column 14 (lines 3-39) of the Georgiou *et al.* (1994) teaching wherein the inventors specify that the particular dosage will simply depend upon the route of administration, host response, and immunogenicity of the insert. Thus, all that is required to obtain the optimal dose is routine experimentation. Appellants have failed to proffer any evidence to the contrary. Appellants' arguments have been carefully considered but are not deemed to be persuasive for the reasons set forth.

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2 Cruse, J. M., and R. E. Lewes, 1995, Illustrated Dictionary of Immunology, CRC Press, pp 21-22.

Response to Arguments

Claims 6, 8-10, 12, and 13 are rejected under 35 U.S.C. § 103(a) as being obvious over Hone *et al.* (1996) in view of Georgiou *et al.* (1994) and Thimmig *et al.* (1993). Applicants traverse and submit that the prior art fails to teach or suggest fusion constructs employing RT. This argument is clearly not persuasive. The examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. *In re Nomiya*, 184 U.S.P.Q. 607 (C.C.P.A. 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. *In re McLaughlin*, 170 U.S.P.Q. 209 (C.C.P.A. 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. *In re Bozek*, 163 U.S.P.Q. 545 (C.C.P.A. 1969). In this case, the prior art clearly provides efficient attenuated enteroinvasive vaccine vectors that induce strong humoral (including mucosal) and cell-mediated immune responses (including T-helper responses) against the immunogen of interest. The prior art clearly illustrates that Lpp-ompA-X fusion proteins are transported to the surface and placed in a highly immunogenic background. Thus, the only real issue is whether one of ordinary skill in the art would have been motivated to prepare RT fusion constructs using these reagents. The answer to this question is emphatically yes. The human

immunodeficiency virus type 1 is the aetiological agent of AIDS. One of ordinary skill in the art would have had more than sufficient motivation to prepare RT fusion constructs because of the medical importance of this virus and gene product. Utilizing the Salmonella expression system would provide a facile means for generating large quantities of an immunogenic protein that will be capable of inducing both humoral and cell-mediated immune response.

Appellants additionally argue that Hone and colleagues fail to disclose a cellular immune response. In support of this argument they reference a portion of the teaching that is directed toward the generation of HIV-1 gp120-specific $CD8^+$ immune responses. First, appellants are reminded that the broadest claims are simply directed toward the generation of a cellular immune response. Additional limitations specify that the response must be a T-helper or $CD4^+$ immune response. Thus, there is no requirement that a strong $CD8^+$ immune response must be generated. Second, the authors clearly state (see abstract, p. 203) that "**surface-expressed rgp 120 is significantly more immunogenic in both the mucosal and systemic compartments than cytoplasmic rgp120...*Salmonella* vectors will be a safe and inexpensive means for delivery of HIV antigens to, and the elicitation of HIV-specific T cells in, the mucosal and systemic compartments**." Strong mucosal IgA immune responses were clearly generated against the OmpA::tgp120 immunogen (see Table 1, p. 205). Third, it is well-known in the field of immunology that B-cells produce antibody in response to activated T-helper

lymphocytes ($CD4^+$).[3] $CD4^+$ lymphocytes become activated when antigen presenting cells (e.g., macrophages) present antigens to their cell surface. There is no question in this study that strong mucosal IgA immune responses were generated. The generation of this type of immune response clearly requires a strong T-helper cell component.

It was further argued by appellants that there is no reasonable expectation of success as suggested by Hone and colleagues. In support of this assertion appellants again rely upon the passage directed toward the generation of HIV-1 gp120-specific $CD8^+$ immune responses. Additional emphasis is placed upon the discussion wherein the authors discuss the optimization of *Salmonella* vectors for the generation of an HIV-1 vaccine. Appellants are again reminded that there is no requirement in the claims that a strong $CD8^+$ immune response against HIV-1 needs to be generated. The claims simply require a cellular immune response be generated. As set forth in one of the dependent claims, this could encompass a T-helper lymphocyte response. Appellants appear to be overlooking a simple fact from this teaching. The authors concluded unambiguously (see p. 205, section 2.3) that "our *Salmonella* vector expressing OmpA::tgp120 elicited high levels of gp120-specific IgA ASC in the LP (Table 1)." The authors also stated (see last paragraph, p. 206) that "the results presented here suggest that HIV-specific immunity **will** be elicited by Salmonella::HIV in the mucosal and systemic compartments." As set forth *supra* in the preceding paragraph, a strong humoral immune response requires a strong T-helper cell

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3 Cruse, J. M., and R. E. Lewes, 1995, Illustrated Dictionary of Immunology, CRC Press, pp 21-22.

immune response as well. Thus, contrary to appellants' assertion, there is a reasonable expectation that administration of a *Salmonella* vector encoding an Lpp::OmpA::RT fusion protein will generate a strong mucosal IgA immune response. A strong T-helper immune response is a prerequisite for such activity.

Appellants further state that the references relied upon fail to teach the claimed dosages (e.g., 10^{12}-10^{14} CFU). Appellants are directed toward column 14 (lines 3-39) of the Georgiou *et al.* (1994) teaching wherein the inventors specify that the particular dosage will simply depend upon the route of administration, host response, and immunogenicity of the insert. Thus, all that is required to obtain the optimal dose is routine experimentation. Appellants have failed to proffer any evidence to the contrary. Appellants' arguments have been carefully considered but are not deemed to be persuasive for the reasons set forth.

Finally, appellants argue that the claims also fail to teach the utilization of *Salmonella* strain SL3261. As clearly set forth in the final rejection of 26 January, 2005, the teachings of Hone and colleagues describes the use of an S. *typhimurium* strain carrying a mutation in the *aro* locus. This attenuated bacterial strain appears to be the same strain described by Fouts *et al.* (1995, Construction and immunogenicity of *Salmonella typhimurium* vaccine vectors that express HIV-1 gp120, Vaccine, 13(17):1697-705) which was designated strain **SL3261**. Since the Patent Office does not have the facilities for examining and comparing appellants claimed S. *typhimurium* strain SL3261 with the S. *typhimurium* strain employed by Hone *et al.* (1996), the burden is upon appellants to demonstrate the

unobvious genotypic/phenotypic differences between the two strains. *In re Best*, 562 F.2d 1252, 195 U.S.P.Q. 430 (C.C.P.A. 1977). *Ex parte Gray*, 10 U.S.P.Q.2d 1922 (Bd. Pat. Appl. Int. 1989). Appellants have failed to proffer any evidence addressing this issue.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

(12) Request to Present Oral Arguments

The examiner requests the opportunity to present arguments at the oral hearing.

Respectfully submitted,

Jeffrey S. Parkin, Ph.D.
Primary Examiner

James C. Housel 2/20/06
Supervisory Patent Examiner
Art Unit 1648

Long Le
Supervisory Patent Examiner
Conferee

09 January, 2006